AstraZeneca

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SENT VIA UNITED PARCEL SERVICE

SEP 27 2000

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir or Madam:

Re: Docket Number 00D-0186
Response to FDA Call for Comments

Reference is made to the International Conference on Harmonization (ICH) Guidance entitled, "Draft Guidance on M4 Common Technical Document."

AstraZeneca Pharmaceuticals LP fully supports the concept of a Common Technical Document, understanding this to mean the submission of the same information to international regulatory authorities. Achieving such would enable exchange of information and decisions between regulatory authorities, a standard by which to judge the time taken to review dossiers and ease of submission. These achievements would result in faster provision of medical developments to the patient using less human resource and process.

AstraZeneca strongly supports the laudable objectives of the CTD as established by the ICH Steering Committee in 1997. The stated goals being: A single, global dossier, a single approach to compiling technical documents and a strong link to the goals of ICH topic M2, the Electronic Submission. AstraZeneca continues to support the following six (6) principles, each of which the company continues to consider, must be met for the CTD to meet its original objectives:

- The CTD must not result in a larger local submission in any territory;
- CTD must not lead to a longer review time in any territory;
- CTD must not lead to or drive toward any negative change in review process;
- CTD must lead to a reduction in the total amount of global documentation for a new product;
- Change control procedures, post approval, are no worse than current with the objective of them being improved; and

00D-0186

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- One set of summary documentation not bigger than the current requirements. Any table of contents listing a summary as required must accept the same summary for all three (3) territorial areas currently involved in the CTD initiative.

AstraZeneca asks that the CTD, as currently presented, be reviewed by the ICH and its associated working parties against the original objectives for the project. An assessment of the perceived benefits should be undertaken against the effects on current regulatory processes. The urgency in time for the delivery of the project should be reviewed. The project must be allowed to continue, without the interim introduction of a compromise, toward the original objective of a Common Technical Document targeted to the major international regulatory authorities. The introduction of a compromise at this stage needs careful assessment of its return, against the risk of disruption to current processes, effect on resources, and the recent technological advances that have overcome many of the immediate issues of regulatory document preparation.

AstraZeneca fully appreciates and is grateful for the tremendous efforts and progress made by the Quality, Safety, and Efficacy working parties and the personal time sacrifice of the individuals involved. The work to date has clarified the hurdles that remain to mutual recognition and shared review process. Significant other benefits have also resulted from progress so far.

AstraZeneca has extensively reviewed the Draft Common Technical Document and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Robert Castor at (302) 886-2594.

Sincerely,

Carol Stinson Fisher

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CSF/mrsc
Attachment

COMMON TECHNICAL DOCUMENT
GENERAL COMMENTS

In the Federal Register Notice, published August 24, 2000, entitled "International Conference on Harmonization; Draft Guidance on M4 Common Technical Document; Availability" the following points were noted:

- Background section, fourth paragraph, fourth sentence, "... will describe an acceptable **format and content** for applications for human pharmaceuticals that, once supplemented with regional particulars, can be used with new products for submission to the regulatory authorities in the three ICH regions."

- Part II, The Common Technical Document, paragraph 2, last sentence, "The draft guidance is not intended to indicate what studies should be included, but merely to indicate an **appropriate format** for data that is submitted."

These two comments appear to be at odds with each other. Please clarify if the intent of the CTD is to provide **format and content** for applications or **just format**. If format only is being harmonized, please explain the advantages of this harmonization for the three ICH regions.

Reference is made in sections below to the Pharmaceutical Education and Research Institute (PERI)-Sponsored Workshop entitled "ICH Common Technical Document (CTD) Workshop" held in Crystal City, Virginia on September 14, 2000. Abbreviated reference to this workshop will be noted as "PERI CTD Workshop."

At the PERI CTD Workshop, Dr. Elaine Esber stated in her keynote address that the CTD is not meant to be a "global dossier." Dr. Esber emphasized that the CTD is not a basis for mutual recognition or a path towards common review practices. In addition, it was noted that all contents will not be harmonized and that the format of the CTD for New Drug Application (NDA) submission would be "one option," with other formats acceptable as per discussion with the appropriate division and /or reviewer. Please clarify how these comments impact ICH's intentions for the CTD. Further, a common document should at least provide insight as to why different review times and concerns are present in different countries when the same "basic" information is submitted to all.

Given that it seems that regional requirements will still be a part of submissions to the three ICH regions, additional region-specific guidance will be required for industry to efficiently use the CTD format. Dr. Charles Hoiberg stated at the PERI CTD Workshop that many FDA guidances will be re-written and others will be forthcoming. AstraZeneca expresses concern about the layers of guidances (ICH and various regional guidances) required to utilize the CTD. Please address the issues surrounding the hierarchy of guidances-ICH has always been the "regulatory ceiling" in the past.

AstraZeneca also requests that ICH publish a guidance that describes the documents that will be replaced by the CTD and those that will remain, clearly delineating required supplements. In the same guidance the intended benefits of the current structure of the CTD should be listed.

Overall, a review of benefit against disruption to current processes should be considered. What is the benefit if the outcome can be a non-mandatory use of the CTD in territories with also more information being required to some regions along with the need for territorial supplements?

COMMON TECHNICAL DOCUMENT
Step 2, Quality Module

MAJOR COMMENTS ON THE QUALITY MODULE

- AstraZeneca requires absolute assurance that the Quality Overall Summary (QOS) will replace the EU Expert Report and Japanese Gaiyo, Sections B and C. At the PERI CTD Workshop, Dr. Esber stated that the Japanese Authorities will not require the Gaiyo if the CTD format is used for submission. Please clarify that "Attached Documents" in the Japanese Submission corresponds to CTD Module 3 (*i.e.,* no territorial supplements).

- Accepting that compromises were necessary to reach Step 2, AstraZeneca wishes to see published lists from all three regions regarding the "additional regional requirements." This is particular in the case for EU and Japan. In addition, we request that the Japanese Authorities comment on the necessity and significance of CTD items which have not been traditionally requested in Japan.

- Sections S2.2 and S6 require considerably more detail than is submitted in EU and Japan and requirement for this level of detail (*e.g.,* weights, equipment) should be challenged strongly. Less detail with regional supplements is more acceptable than more information required for all, but this strongly negates the original purpose of the CTD.

- Reference is made too strongly to drug substance expiry date (*e.g.,* QOS Section 7, S7.1). It should be rare to assign an expiry date to drug substances-see Q1A.

- With reference to Module P 3.5-Process Validation and/or Evaluation, please clarify that the process validation referenced here is not "GMP Process Validation" which, in the US, is part of the field investigation. Dr. Hoiberg stated at the PERI CTD Workshop that this module was designed to be a "place holder" for regional validation requirements. AstraZeneca requires absolute assurance that the validation submitted in this module would be data meant for center review and not "GMP field process validation."

- Excipients of Human or Animal Origin, Module P4.5, primarily applies to biotech products, but would represent a new filing requirement for NCEs for excipients such as magnesium stearate. Previously, we would have "BSE certificates" etc., on hand for field inspection.

- Module P4.6, Novel Excipients, represents a new US requirement for NCEs. We suggest this module be addressed in the regional requirements.

- A module addressing "site specific stability," for the US is not apparent. If the manufacturing facility/site for the NCE or biologic began at a pilot plant and will be transferred to a commercial site, then issues surrounding "site specific stability" come into play. For this type of change, certificates of analysis from three commercial scale validation batches provides assurance that the technology transfer is complete from pilot to commercial site. Please provide guidance on how to file this information.

MINOR COMMENTS ON THE QUALITY MODULE

- Q6A refers to Control of Materials (starting materials etc.). However, it does not apply *per se* to Sections S2.3 and S2.4. The same rigors of detail of method description and specification justification applicable to drug substance and drug product should not be required or suggested for starting materials and intermediates.

- Reference to Q2A and B, Method Validation, should be included in Sections S7.3 and P7.3.

- "Working Capacity" of drug product manufacturing equipment in P3.3 should not be omitted.

- Wording in S6 and P6 requires careful review, especially repeating large sections. It is highly unusual for drug products to be "reactive" and hydroscopic is hardly "reactive."

- In the Pharmaceutical Development Module, P2, a note about providing a rationale for using a sterile processing method other than terminal sterilization should be added to Section 5, Microbiological Attributes.

- A module for Comparability Protocols (US, R3) is provided. Current FDA guidance addresses comparability protocols only to biological/biotech products within the jurisdiction of CDER or CBER.

- Reference is made to submission of data for sterilization process validation for drug substances intended to be used for NCEs. Currently, there is no FDA Guidance provided on this subject. Please clarify that the sterilization process validation discussed here does not translate, for drug substances, into the detail required for drug products under FDA Guidance "Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products."

- Please confirm that modules for US labeling and environmental assessment will be included in M1.

- AstraZeneca suggests changing the title of the regional information Section, R4, Process Validation Protocol of the Drug Product (EU) to "Summary of Critical Parameters for Proposed Process Validation of Drug Product," R4.

COMMON TECHNICAL DOCUMENT
Step 2, Non-clinical Safety Modules

GENERAL COMMENTS ON THE NON-CLINICAL SAFETY MODULE

It is stated that the primary purpose of the Non-Clinical Executive Summary (Section A) is to provide a comprehensive review of the non-clinical data and should include the clinical relevance of the findings, cross-linking with chemistry/pharmacy, and discussion relating to the proposed prescribing information. The non-clinical executive summary should also present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the drug substance/product. Finally, appropriate relevant scientific literature should be included in this Executive Summary. More detailed summaries of each of the subsections of the nonclinical disciplines and individual study tables should be in IIB1 and IIB2, respectively.

Representatives from AstraZeneca that have reviewed the non-clinical safety modules support the principles of the CTD provided that the document is accepted in full and with no additions. Any table of contents, listing a summary as required, must accept the same summary for all three territorial areas currently involved in the CTD initiative. Our understanding is that the Expert Report will still be required for European submissions, but since a critical assessment is to be presented in the Executive Summary of the CTD, we feel that this summary could replace the Expert Report.

MAJOR COMMENTS ON THE NON-CLINICAL SAFETY MODULE

- Tables may be added to the text, as appropriate, in order to assist in the description of data, however, in the guidance the main study tables are in a separate section. This format requires the reviewer to flip back and forth from text to tables. We suggest including the tables at the end of each summary section for ease of use.

- In the DMPK summary, a short paragraph with Chemical descriptions (*e.g.,* structure, pKa, logP, solubility, etc.) is needed to give the reader a better understanding of the DMPK outcome.

- With regards to the DMPK section, why is the intended route of administration described first? In order to understand the pharmacokinetics (PK) of a compound, you have to know the basic PK, which means we should describe the intravenous route first

(assuming it can be dosed that way). The IV route gives the platform for the remaining routes.

- No table was found for the in vitro absorption, stability studies in different fluids, and tissues.

- On page 13, part 3.4.8, Other Toxicity Studies, dependency studies were listed in this section. Since dependency studies are usually conducted as pharmacology studies in the USA and Europe, the study should be described in the Pharmacology section.

- On pages 49-50, Appendix B, there is a footnote for single-dose and repeat-dose toxicity that states that the NOAEL should be underlined. As a NOAEL has not been requested for single dose studies, "single-dose toxicity" should be deleted.

- The CTD requires NOAEL even for single-dose toxicity studies. The current guideline does not request determination of NOAEL in single-dose toxicity studies. Is it permissible to just show an observed maximum non-lethal dose?

- In Appendix B, there was concern that the non-clinical toxicokinetics overview would be required, and there is a request that this table be deleted or stress that this table not be routinely required.

- The number of summaries (overall followed by specific sections) and overall conclusions will be similar and therefore the document may become very repetitive.

- In the Single-Dose Toxicity Table, the English term "observed maximum non-lethal dose" was translated as "maximum-tolerated dose" in Japanese. These two terms have different meanings and maximum-tolerated dose is not required in the guideline. Please assure that translated terms convey the intended meaning.

- When antigencity and/or dependency studies are not conducted, the reasons for not conducting the studies are explained in the Gaiyo. Please clarify that the CTD does not require an indpendent section to explain the reasons for not conducting antigenicity and/or dependency studies.

- In example 3D, Toxicology Batches Used Table, information on the batches used in preliminary dose-finding studies was included. With reference to the Japanese market, dose finding studies are somethimes conducted under non-GLP conditions and often not used as pivotal data but as reference data. Please clarify if we are required to list the batches used in all of the toxicology studies in the CTD. In the example cited above, the information was given for drug substance; please confirm that this information is also required for drug products. What overlap, if any, does the toxicology section have with the Quality Module, S4.4 "Analysis of Batches"?

- In Section 3.2, The Pharmacology Written Summary, "other pharmacology studies" should be listed here, as is, the other "PK and Tox Studies." We suggest establishing a new Section 3.2.6 to include the following:

  3.2.6 Other Pharmacology Studies
  -Studies on Stereoisomers
  -Studies on Metabolites
  -Studies on Impurities
  -Other Studies

Similarly, we suggest inserting new Sections "B.1.1.5 Other Pharmacology Studies," "1.1.3 Pharmacodynamic Drug Interactions" and "1.1.4 Other Pharmacology Studies," as appropriate.

- With specific reference to animal PK studies, we suggest the following:

  -The CTD lists PK parameters as Cmax, Tmax, AUC and t 1/2. Other PK parameters (C,Vd etc.) should be included.

  -The guidance states that AUC and/or t 1/2 should be described for a tissue distribution study. We challenge this point.

  -The guidances states that determination of unchanged substance in major organs should be described for a tissue distribution study. This is a difficult task.

  -Since necessity of quantitative data of metabolite analysis is increasing, the recovery in analysis process will be important.

COMMON TECHNICAL DOCUMENT
Step 2, Efficacy Modules

GENERAL COMMENTS ON THE EFFICACY MODULE

Early drafts of this document contained a statement at the beginning that explained that these guidelines should not be used as a template for the presentation of actual CTD submissions, and that applicants should structure and present their submissions as appropriate to their application. This statement is not in the latest version, although similar comments are made at certain points in the document. This up-front advice on presentation should be put back into the document.

We are very pleased to see that on the whole there is no mention of additional territorial supplements, apart from a reference in Section 4 of the Written Summaries (see comment below). We presume and hope that this philosophy of one set of documentation for every authority with no supplements will be maintained in the final version of these guidelines.

In general, we believe that this current draft of efficacy guidelines provide for a well-rounded, comprehensive dossier that provides more than adequate information for review.

COMMENT ON CLINICAL OVERALL SUMMARY

We suggest that the COS should have a summary of proposed Prescribing Information, possibly as part of the Benefit and Risk Section.

MAJOR COMMENTS ON WRITTEN SUMMARIES

- It would be very useful to provide a statement at the beginning of the guidelines on the summaries, advising applicants that the summaries should not contain discussion of data. Any issues that need discussion should be dealt with in the Clinical Overall Summary.

- During discussion at the PERI Workshop on the CTD, Dr. Robert DeLap noted that for many applications a separate Integrated Summary of Efficacy (ISE) may not be needed. This information could go in the Written Summaries. He also stated that, if analysis of efficacy data demonstrated an incompatibility with the CTD format, a separate report might be required. Please clarify if guidance is or will be available to analyze whether or not efficacy data should go in the Written Summaries or in a separate ISE. We support the streamlining of ISE information into the Written Summaries of the CTD and would also like confirmation from the FDA of the same.

- With reference to the Background and Overview Sections (1.1, 2.1 and 3.1), please clarify that these sections should provide an overview and a rationale for the program of studies in these categories, not more narratives of individual trials.

- The narrative summaries (Sections 1.2, 2.1 and 3.1) should be reference documents. As presented in the current CTD version, these summaries would need to be read from beginning to end. Overall, the narrative summaries are redundant; the current structure requires that individual trials be summarized in at least four different places.

- With reference to Section 3.3.1 Study Populations:

    - Bullet three asks for discussion of the impact of differences. It is completely inappropriate to have this discussion in this section or any other part of the summary. If issues need to be addressed, this should be done in the Clinical Overall Summary.

    - Clarify that this section is describing the "efficacy patient population," it would be useful to provide a flow chart showing how total population is subdivided into other categories (*e.g.,* per protocol, ITT etc.).

    - Suggest that baseline characteristics needed are specified.

- Section 3.4.1, Evidence of Long-Term Efficacy and/or Tolerance Effects should not be a separate subsection of 3.4. We suggest that this section either be part of 3.4 or listed as 3.5.

- With reference to Section 3.4, the section describing statistical analysis of clinical trial information regarding recommended dosage and administration, we have the following concern: The CTD states that "the rationale for difference in dose-response relationships attributed to age, physical constitution, sex, disease, or other factors should be described." However, if we try to evaluate dose-response relationships stratified by each factor, the number of subjects per group would be very small, thereby increasing a probability of incidentally producing numerically contradictory data. Caution should be exercised not to make any forced medical interpretation under such circumstances. We suggest including warning text about these circumstances such as, "when data from a small number of subjects are discussed, the probability of incidentally having such results should be taken into consideration."

- The value of Section 4., The Integrated Analyses of Safety that are Routinely Submitted in Some Regions, is questioned, as this would only require extra work for applicants with no apparent value.

- In the US an Integrated Summary of Safety (ISS) will still be required as a separate piece of the submission. We challenge this as the headings required in the ISS are covered in the Overall Summary. Also, please clarify the FDA's plans for revising the guidance for ISS and how a new guidance would impact the CTD.

- In Module V it is stated that a report on "analysis of data from more than one study" should be attached, if necessary. Please clarify if this means a "statistical report" or a report separately summarized.

- Clinical Trial Reports are to be attached to Module V. Please clarify if it is permissible to attach only the text portion or if the entire report, with appendices, should be attached.